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Autonomic dysfunction in heart failure and renal disease

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In the clinical settings of heart failure and chronic kidney disease, autonomic dysfunction is increasingly being recognized as having direct detrimental effects (Klein et al., 2003; May et al., 2010; Schwartz and De Ferrari, 2011). More broadly across the fields of cardiovascular and renal disease, research efforts are being directed toward understanding the mechanisms that bind complex interactions between the autonomic, cardiovascular, and renal systems. The ultimate goal being the identification of innovative diagnostic and treatment approaches that limit hypertension and target end organ damage. Our increasing knowledge of the role of the central renin angiotensin system (RAS) in mediating autonomic function (Zucker et al., 2009) and current developments in renal denervation as a treatment for resistant hypertension are examples of this (Krum et al., 2009; Esler et al., 2010). This Frontiers Research Topic brings together original research, methods, and review articles to provide an overall perspective on this interaction. These manuscripts serve to highlight not only the critical role of the autonomic nervous system, but also the potential usage of non-invasive measures of sympathetic and parasympathetic outflow as diagnostic and predictive tools.

As reviewed by Hildreth (2011), in patients with renal disease, sympatho-vagal imbalance (namely increased sympathetic and decreased parasympathetic function) is a prognostic indicator of cardiovascular mortality, as measured using the autonomic indices of heart rate variability (HRV), baroreflex sensitivity (BRS), and baroreceptor reflex effectiveness index (BEI). A comparison of studies utilizing various measures of HRV and baroreflex function in end stage renal disease patients show that a progressive decline in renal function can be correlated with a reduction in these parameters. Hildreth (2011) hypothesizes that this may be due to peripheral changes, such as vascular stiffness, or alternatively, abnormal central processing or an inability of the cardiac autonomic efferents to effectively control heart rate. The major role of the kidneys in driving autonomic dysfunction and subsequent cardiovascular disease is highlighted by studies that show renal transplantation results in an improvement in HRV parameters (Yang et al., 2010).

The association between autonomic dysfunction, as determined using HRV parameters, and increased risk of mortality and morbidity in cardiovascular disease is further demonstrated in the original research article by Norman et al. (2012). Using a model of acute cardiac arrest in the mouse, the authors demonstrate an inverse linear relationship between HRV and measures of neuronal cell damage and microglial activation in the hippocampus. While further work in this area is required to establish causality, this study raises the exciting possibility that HRV can be used as a non-invasive measure to determine and monitor neuronal damage after cardiac arrest and global cerebral ischemia.

In the methods paper presented by Reulecke et al. (2012), autonomic function is examined in healthy preterm neonates, applying HRV to cardiorespiratory data using non-linear methods. Reference HRV data is currently only available for adults (Taskforce, 1996), but through a complex series of analyses, Reulecke et al. (2012) show that while the relationship between heart rate and respiration in preterm infants is not fully developed, there is a difference in the degree of control during quiet and active sleep states, with the quiet state demonstrating an increased degree of vagal modulation or activity. This study provides a clear step forward in our knowledge of the development of autonomic function in humans. It further highlights the potential application of HRV as a way of monitoring this critical subgroup of patients for disorders of the cardiovascular and respiratory systems, and as used in adults, predicting cardiovascular risk (Voss et al., 2006).

The central mechanisms that may drive autonomic dysfunction in heart failure, and specifically increased sympathetic outflow, are reviewed in the paper by Campos et al. (2011). The role of the brain RAS is examined, with an extensive review of the authors previous studies using the [TGR(AsrAOGEN)] transgenic rat, where just brain angiotensinogen is inhibited (Schinke et al., 1999). These animals show a number of differences to control animals under baseline conditions, including low blood pressure and diabetes, but most notably, under imposed cardiovascular disease such as myocardial infarction, sympathetic hyperactivity is markedly attenuated in the transgenic animals, alongside reduced left ventricular remodeling (Wang et al., 2004). This body of work supports pharmacological targeting of brain RAS as a treatment option for disorders characterized by autonomic dysfunction.

In the review provided by Schlaich et al. (2012), the topical issue of renal denervation is reviewed by the pioneers of this approach. This treatment is receiving marked scientific and community interest, and has opened up not only an exciting therapeutic option but also consolidated our appreciation of the critical role renal afferents play as drivers of central sympathetic outflow. The review article looks further into the links between sympathetic outflow and glucose metabolism, with data presented from a group of patients who, after renal denervation, show improved fasting glucose, insulin, and C-peptide levels, in addition to reduced insulin resistance (Mahfoud et al., 2011; Schlaich et al., 2012). The benefits of renal denervation are therefore not limited to blood pressure control alone, and in line with the theme of this Frontiers Research Topic, the authors conclude that patients with chronic kidney disease or heart failure may also be suitable candidates for this approach. Indeed, a recent pilot study assessing renal denervation in patients with moderate to severe renal disease indicates not only a reduction

in blood pressure in these patients, but indications of improvement in other clinical markers including hemoglobin levels and peripheral augmentation index (Hering et al., 2012).

The broader implications of renal denervation as a therapeutic option are still under consideration, and this is addressed in the review by Vink and Blankestijn (2012), who raise questions regarding the wide range of responses amongst patients after renal denervation and the mechanism(s) responsible for non-responders (Esler et al., 2010). Questions are also posed as to how best monitor the intervention. As highlighted in their review (Vink and Blankestijn, 2012), the kidney is both a generator and recipient of sympathetic activity, with increased sympathetic activity being an early event in the pathophysiology of renal failure that correlates with disease severity. Autonomic dysfunction is a key feature therefore, and as described by Hildreth (2011), measures such as HRV or BRS/BEI may prove to be clinically viable approaches by which to not only assess autonomic function after renal denervation, but also be a valuable long term measure for monitoring outcomes.

In conclusion, this Frontiers Review Topic will hopefully serve to provide an comprehensive overview of the critical role played by the autonomic nervous system in heart failure and renal disease, and stimulate interest in how determination of autonomic dysfunction can be applied both as a measure of risk and a specific target for treatment options.

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